

### **REMARKS**

Claims 1, 3, 6-7, 17, 20-23, 26-27, 29-30, 32, 36, 42-49, 63-76, 78, and 81-84 constitute the pending claims in the present application. Applicants cancel, without prejudice, claims 23, 26, 45, 46, 65, 74-76, 84. Applicants add new claims 92 and 93. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants acknowledge election of the invention of group I for prosecution on the merits. Claims 1, 3, 6-7, 17, 20-23, 26-27, 29-30, 32, 36, 42-49, 63-76, 78, and 81-84 are under consideration.

2. The title is objected to for allegedly failing to be sufficiently descriptive. Applicants' amendment to the specification to provide a more descriptive title is believed to obviate this objection. Reconsideration and withdrawal of this objection are respectfully requested.

3. Claims 34 and 47-49 are objected to as depending upon a canceled base claim. Additionally, claims 68 and 69 are objected to under 37 CFR 1.75(c) as being in improper form. Applicants' amendments to the claims are believed to obviate these objections.

4. Claims 1, 3, 6, 7, 17, 20-23, 27, 29, 30, 32-36, 42-49, 63-76, 78, and 81-84 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Claim 1 has been amended to recite a cell-based assay, and the rejected independent claims have been amended to recite cells that transduce intracellular signals of the hedgehog pathway, thereby obviating rejections on these grounds.

As to the rejection of claims 23, 74, and 84 for allegedly lacking description of the transcriptional regulatory sequences, Applicants submit that these sequences are described sufficiently in the specification to indicate that Applicants were in possession of the invention at the time of filing. Applicants direct the Examiner's attention to page 64, line 3 – page 66, line 20 which clearly supports the presently claimed invention. The Written Description Guidelines for

the Examination of Patent Applications state that “whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors.” The factors which should be considered include “level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.” Written Description Guidelines for the Examination of Patent Applications, section II, page 1106, column 2 (See also MPEP 2163).

Applicants submit that the specification meets these criteria, thus satisfying the above guidelines. Specifically, the specification provides a detailed functional and structural description of the hedgehog pathway including, but not limited to, the functional and structural role of GLI in the hedgehog pathway, the usefulness of GLI expression as an indicator of signaling via the hedgehog pathway, and the usefulness of a GLI reporter construct as an indicator of signaling via the hedgehog pathway (page 64, line 3 – page 66, line 20).

Furthermore, at the time this application was filed, the presence of positive and negative regulatory sequences was understood by one of skill in the art to be a feature of prokaryotic and eukaryotic genes in general, and a feature of genes in the hedgehog/patched pathway specifically. In accordance with the written description guidelines and the MPEP, “[i]nformation which is well known in the art need not be described in detail in the specification.” Written Description Guidelines for the Examination of Patent Applications, section II, page 1105, column 3; MPEP 2163.

Moreover, Applicants point out that the identification and sequencing of the distinct negative regulatory region or regions is not necessary to practice the claimed invention. As long as the negative regulatory elements are present somewhere within the constructs used to carry out the methods of the present invention, their precise location and sequence is not needed to perform the claimed methods. This point is most effectively illustrated by an examination of the endogenous genes of living organisms. Non-coding regions *in vivo* contain both positive and negative regulatory elements, often located in close proximity. Such elements need not be present in isolation from the context of other elements in the non-coding region in order to

regulate expression of the particular gene. Similarly, in the claimed invention, regulatory elements need not be isolated from the remainder of the non-coding region to function. Applicants' methods can be effectively practiced using non-coding sequences including both positive and negative regulatory elements, the precise location of which may or may not be known, or can be practiced using specifically identified regulatory elements within the non-coding sequence. Applicants note that in accordance with the written description guidelines, "[i]f a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met."

For these reasons, Applicants maintain that the matter of claims 23, 74, and 84 is supported in the specification with sufficient detail that one of skill in the art would recognize that Applicants were in possession of the claimed invention. The presence of both positive and negative regulatory elements within the non-coding regions of genes is a characteristic of gene regulation well appreciated by those of skill in the art, and Applicants note that the methods claimed require only the presence of a regulatory region, not its identification or sequencing. This, in light of the detailed description provided in the specification and the high level of skill in the art of molecular and developmental biology, demonstrates that Applicants were in possession of the claimed invention and satisfy all of the requirements under 35 U.S.C. § 112, first paragraph.

Claims 45 and 46 have been cancelled, thereby rendering the rejection of these claims moot.

For the reasons presented above, Applicants respectfully submit that the claims as amended fully comply with the written description requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of this rejection are respectfully requested.

5. Claims 1, 3, 6, 7, 17, 20-23, 27, 29, 30, 32-36, 42-49, 63-76, 78, and 81-84 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Several of the grounds for rejecting the claims for lack of enablement parallel grounds addressed above with respect to the written description requirement. Applicants submit that the amendments and arguments detailed above adequately address the present enablement rejection.

Applicants have amended claims 17, 63, and 78 to recite naturally occurring patched proteins as the Examiner has suggested, thereby obviating the Examiner's rejection.

For the reasons presented above, Applicants submit that the claims as amended fully comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of this rejection are respectfully requested.

6. Claims 1, 3, 6, 7, 17, 20-23, 27, 29, 30, 32-36, 42-49, 63-76, 78, and 81-84 are rejected under 35 U.S.C. 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Claims 1, 17, 30, and 78 are objected to because the term "statistically significant" is allegedly unclear. Applicants respectfully disagree. Nevertheless, to expedite prosecution, Applicants have amended the claims to delete reference to the term "statistically significant." Applicants' amendment is not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Claim 7 has been amended to remove the word "substantially," thereby rendering rejection of this claim moot.

Claims 17, 63, and 78 have been amended as suggested by the Examiner.

Claims 21-23, 48, 65, and 82-84 are rejected for "improper Markush language." Applicants respectfully direct the Examiner's attention to MPEP 2173.05(h), "Alternative Limitations." Although this section begins with a discussion of Markush groups, it continues to discuss the use of other ways of setting forth alternatives. Applicants submit that these claims as amended are completely consistent with MPEP 2173.05(h) II, "'Or' Terminology. If the Examiner wishes to maintain this rejection, Applicants respectfully request an explanation of what exactly it is that is unclear or indefinite about these claims. Applicants submit that the

amendment from “and” to “or” also addresses the rejection of claim 23 in particular in the subsequent paragraph.

Claim 29 has been amended to remove the recitation of “homologs,” thereby rendering the rejection on this basis moot. Claim 29 has been further amended to clarify that the heterologous gene constructs are expressed.

Claim 30 has been amended as suggested by the Examiner.

Claim 47 has been amended to remove the term “variegated,” thereby rendering the rejection on this basis moot. Claim 47 has been further amended to clarify that the library is being screened. Applicants submit that one of skill in the art would not have understood this claim, either in its original form or as amended, to require repeating the assay 100 times on each compound.

Claim 49 has been amended to clarify how the pharmaceutical composition is prepared. Applicants submit that the indication in claim 49 that the compound is “identified” makes it quite clear that the assay must first be performed to identify such a compound, and that one of skill in the art would understand that the step in claim 49 is to be performed after the steps of the assay claims upon which it depends, or else the compound could not have been “identified.” If the Examiner still believes this claim to be unclear, Applicants respectfully request that he suggest a suitable amendment.

Claim 63 has been amended as suggested by the Examiner.

Applicants’ cancellation of claim 65 renders the rejection moot.

Claim 70 has been amended to eliminate the recitation of “comparing the response of said cells to a test agent.” Applicants submit that, together with the amendments to claim 63, these amendments render claim 70 clear and definite.

Claim 71 has been amended to clarify how the reporter gene product is detected. Claim 72 has been amended to clarify the meaning of “intrinsic activity.” Although Applicants submit that the meaning of this term is sufficiently clear from the description in the specification on

page 65, Applicants have amended this phrase to clarify its meaning. Claim 73 has been amended as suggested by the Examiner.

Applicants' cancellation of claims 74-76 renders rejection of these claims moot.

Claim 78 has been amended to clarify the role of "a hedgehog protein."

For the reasons presented above, Applicants submit that the pending claims are fully compliant with 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of this rejection are respectfully requested.

7. Claims 1, 3, 6-7, 17, 20-23, 26-27, 30, 33-36, 42-44, 46, 63-64, 66-70, 74, 78, and 81-84 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Scott et al., US Patent No. 5,837,538. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Applicants have amended the claims to more particularly point out certain embodiments of the invention. Specifically, the amended claims are directed to screening methods in which expression of GLI or of a GLI reporter construct are examined. The cited reference fails to teach or suggest assays based on the detection of GLI or of a GLI reporter construct, and thus the cited reference fails to teach or suggest each and every limitation of the claims. Accordingly, the cited reference fails to anticipate the claimed subject matter. Reconsideration and withdrawal of this rejection are respectfully requested.

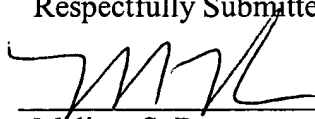
8. Claim 65 is rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Scott et al. in view of Niswander et al. Applicants traverse this rejection.

As outlined in detail above, Applicants' amendments to the claims render moot the rejection based on Scott et al. Additionally, Applicants' have cancelled claim 65, thereby obviating the rejection.

### CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. HMSU-P14-006.**

Respectfully Submitted,



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